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Operative vs. Non-Operative Treatment of Acute Appendicitis

By

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Introduction

Appendicitis is one of the most common medical emergencies worldwide. Surgical removal of the appendix through appendectomy has been the definitive standard of care since the 19th century[1]. However, due to the potential complications of surgery, researchers have begun to investigate a more conservative treatment of appendicitis through the use of antibiotics alone [2–6]. The aim of this paper is to analyze antibiotic usage in treatment of acute appendicitis in order to determine if it is a viable treatment and possible alternative to appendectomy. The following Population, Intervention, Comparison, Outcome, and Time (PICOT) question will be investigated: How effective is antibiotic administration for the treatment of acute appendicitis compared to surgical appendectomy?

Pathophysiology

The complex pathophysiology of appendicitis is beyond the scope of this paper, however will be discussed in brief. The appendix is a luminal structure located at the distal end of the cecum of the large intestine. Appendicitis occurs when a fecalith, inflammation of the tissue, or malignancy causes an obstruction of the appendix [7]. This obstruction leads to an increase in appendiceal intraluminal pressure, causing inflammation, thrombosis, and occlusion of blood vessels. Additionally, obstruction can also result in bacterial overgrowth, most commonly *Escherichia coli, Bacteroides fragilis, Psuedomonas, and Peptostreptococcus.* The increased pressure, thrombosis, and bacterial overgrowth cause nerve stimulation, and abdominal pain occurs as a result. If the blood vessels are occluded long enough, this can lead to ischemia of the appendix and eventual necrosis [8]. If the inflammation and ischemia are not relieved, the appendix is at risk of perforation.

Epidemiology

Acute appendicitis has a lifetime prevalence of 7-8% and is one of the most common medical emergencies in the world [9]. It is more common in males than women, with 8.6% lifetime risk in men compared to 6.9% in women [8] Appendicitis is more likely to occur in the second and third decades of life, however is also seen in children and adolescents [8]. Appendiceal perforation occurs in approximately 13-20 percent of acute appendicitis cases. Perforation is more common in men than women and usually occurs in older adults as opposed to children [8].

Clinical Presentation

Although clinical presentation for appendicitis can vary, most patients generally present with epigastric pain that eventually localizes to the right lower quadrant. Nausea, vomiting, and fever are also common. There are several physical exam findings consistent with the diagnosis of appendicitis. McBurney's Point is located approximately 2/3 the distance from the umbilicus to the anterior superior iliac spine. Tenderness over this point has a specificity of 75-86% for appendicitis [8]. Additional physical exam maneuvers include Rovsing's sign, which is right lower quadrant pain that occurs as a result of palpation of the left lower quadrant. The psoas sign can be seen when right lower quadrant pain occurs with right hip extension. Laboratory studies will often reveal leukocytosis. Although these physical exam and laboratory findings can increase a clinician's suspicion for acute appendicitis, diagnosis is confirmed through a computed tomography (CT) scan showing inflammation of the appendix [8].

Treatment

If left untreated, appendicitis can progress to a severe life-threatening infection and even result in death. The standard treatment of appendicitis is removal of the appendix through appendectomy. As with any surgery, there are risks associated with appendectomy, which include damage to surrounding structures, adhesions, infection, hemorrhage, and in rare cases even death [10]. However, recent research has emerged investigating the effects of antibiotic treatment opposed to appendectomy for the treatment of appendicitis. In light of this emerging research, this paper will further investigate how effective antibiotic administration alone may be in treating appendicitis versus traditional surgical appendectomy.

Methods

PubMed, Cochrane Library, and Google Scholar were utilized in order to further investigate the PICOT question stated in the first paragraph above. The primary search terms utilized were “Appendicitis”, “Antibiotics”, and “Appendectomy”, and the search was further refined to include alternative terms, including “Appendix”, “Medications”, and “Treatment”. PubMed was further narrowed by excluding all research except for systematic reviews published after 2015. Articles were further filtered to include only articles that had at least a one-year follow up with patients. Any systematic review that did not have quality evaluation of the studies was also excluded. Additionally, uptodate.com was used as a resource to locate additional information regarding appendicitis. The citation tool, F1000, was used to organize the research articles and systematic reviews utilized in this paper. The systematic reviews were critically analyzed using the GRADE bias evaluation.

Results

Summary of Individual Studies, Methods, and Results

Rocha et al (2015) reviewed 8 meta-analyses investigating the effects of antibiotics versus appendectomy in the treatment of acute appendicitis in adults >18 years old (Table 1)[11]. The data was analyzed using and mean, standard deviation, odds ratio, and confidence interval. The mean number of patients in the primary antibiotic therapy group was 403 ± 74, while the mean number of patients in the appendectomy group was 453 ± 163 patients. Table 1 below lists the details of the meta-analyses included in this review. Imaging modality was not specified for each study, however it was noted that most studies used ultrasound while some utilized CT. Antibiotics were also not specified for each systematic review analyzed, however they did vary widely within the studies.

Minor complications measured in the results included prolonged post-operative course, diarrhea (including C. diff infection), fungal infection, and minor wound infection. Major complications included thromboembolism, major wound infection, reoperation, small bowel obstruction, abscess formation, or peritonitis. 7 out of the 8 studies included in this meta-analyses found that treatment with antibiotics had decreased minor and major complications. The treatment group with antibiotics had faster resolution of inflammatory markers, which were defined as neutrophil count, C-reactive protein, and temperature curve, and required less pain medication. The treatment group with antibiotics was able to return to work sooner compared to the group treated with appendectomy (95% CI -6.99, -3.40 days). In regards to efficacy of treatment, the researchers found that appendectomy was more effective than treatment with antibiotics (95% CI 4.37, 8.46)[11]. Researchers did not clarify how treatment efficacy was calculated but reported it was based upon overall treatment of appendicitis. Interestingly, from 24-48 hours both treatments were equal in their rate of failures (95% CI .94, 6.33). Rocha et al 2015 found that overall there was no difference in length of hospital stay between treatment with antibiotics versus treatment with appendectomy, however one systematic review did find that appendectomy had a 34% decrease in length of stay (95% CI 0.44, 0.87). Only one study investigated cost, which found that antibiotic therapy had a decreased cost of less than $1257 compared to treatment with appendectomy. Of note, the majority of studies investigated used open appendectomy as opposed to laparoscopic. A summary of the outcomes and favored intervention can be seen in Table 2. Quality of the studies was investigated in a variety of ways, including Mean Jadid Score, NOQAS, and GRADE system. The overall quality of the studies ranged from poor-low moderate based on the various evaluations used (Table I in appendix).

Table 1. Rocha et al Meta-Analyses Comparing Antibiotics versus Appendectomy in Patients Acute Appendicitis.

Author (Year)	Participants	Number of RCTs Included	Imaging Modality for Diagnosis	Risk of Bias
Varadhan et al (2010)	661 (350[a], 311[s])	3	Ranged from Clinical, laboratory tests, ultrasound (US), CT	Variable antibiotic usage, variations in randomization, selection bias, crossover to surgery
Liu et al (2011)	1201 (433[a], 786[s])	6	Ranged from Clinical, Laboratory tests, US, CT	Variable antibiotic usage, selection bias
Ansaloni et al (2011)	741 (390[a], 351[s])	4	Ranged from Clinical, Laboratory tests, US, CT	Variable antibiotic usage, unclear randomization, protocol violations
Wilms et al (2011)	901 (415[a], 486[s])	5	Ranged from Clinical, Laboratory tests, US, CT	Variable antibiotic usage (including oral vs. IV), selection bias,
Mason et al (2012)	980 (510[a], 470[s])	5	Ranged from Clinical,	Variable antibiotic

			Laboratory tests, US, CT	usage, selection bias
Varadhan et al (2012)	900 (470[a], 430[s])	4	Ranged from Clinical, Laboratory Tests, US	Variable antibiotic usage
Liu et al (2014)	983 (391[a], 592[s])	5	Not Specified	Variable antibiotic usage
Kirby et al (2015)	531 (268[a], 263[s])	3	Ranged from Clinical, Laboratory tests, US, CT	Variable antibiotic usage, no prophylactic antibiotics with surgery

Based on table taken from Rocha et al page ***8

a: appendectomy, s: surgery

1. Mean Jadad Score 2. NOQAS 3. GRADE system

Table 2. Rocha et al Outcome Measures and Overall Conclusion

Outcome	Author Conclusion
Treatment Efficacy	Appendectomy Favored
Complications	Antibiotics Favored
Failure of Treatment	Appendectomy Favored
Readmissions	Appendectomy Favored
Length of Hospital Stay	No Difference
Return to Work	Antibiotics Favored

Findlay et al (2016) investigated six randomized control trials (RCT) comparing antibiotics versus appendectomy for the treatment of acute appendicitis in patients aged 16 years old or greater[12]. The six reviews comprised 1,724 patients aged 18 years and old - 837 patients were randomized to the antibiotic treatment group and 887 to the surgical appendectomy group (Table 3). All of the studies included had a follow-up of at least one year.

The authors investigated length of stay between the two groups and found that antibiotics were associated with a longer length of hospital stay (95% CI 0.10 to 0.85 days). Length of sick leave was shorter with antibiotics (-2.13 days) compared to appendectomy (95% CI -3.85 to -.41)[12]. Pain was measured at multiple time points using the visual analogue scale. Vons et al found no differences in pain between the treatment groups while Hansson et al reports increased duration of pain with appendectomy. Salimen et al reported more pain after being discharged from the hospital and at 1 week follow up in the same treatment group. Eriksson et al found less morphine consumption with patients assigned to the antibiotics group. Inflammatory response was also investigated in this study[12]. In contrast to Rocha et al, Eriksson et al reports no difference in C reactive protein between the appendectomy and antibiotic group. However, Erikson et al did find white cell count was reduced in the group receiving antibiotics compared to the group who received appendectomy. Cost of treatment was only reported in two studies – Hansson et al found lower costs with antibiotics, while Turhan et al found no difference. Outcome measures can be seen below in Table 4. Overall quality of studies was assessed using the GRADE tool. The overall study quality was found to be very low (Table II in appendix) [12]. Out of the six studies investigated, Findlay et al found no difference in complications between treatment with appendectomy versus antibiotics. Of note, reported complications were highly variable within the studies included, and the authors noted a high risk of reporting bias within the studies. The quality of studies was analyzed based on the GRADE bias evaluation (Table II in appendix)

Table 3. Findlay, et al Study Characteristics

Author, Year	Population	Imaging Modality for Diagnosis	Antibiotics	Risk of Bias

Salminen, 2015	530 (257[a], 273[s])	CT	Ertapenem IV x 3 days, Levofloxacin + Metronidazole x 7 days after discharge	No postoperative antibiotics (even with evidence of contamination), age >60 years old or significant systemic illness excluded
Vons, 2011	143 (123[a], 120[s])	CT	Co-amoxiclav po/iv >1d, co-amoxidav PO x 8 days after discharge	Oral antibiotics used except if the patient was nauseous or vomiting
Hansson, 2009	369 (202[a], 167[s])	Clinical +/- US/CT	Cefuroxime + Metronidazole IV (>1d), Ciprofloxacin + Metronidazole PO after discharge	Cross-over allowed after randomization if patient/surgeon requested
Turhan, 2009	290 (107[a], 183[s])	Clinical + US/CT (only antibiotic group)	Ampicillin + Gentamicin + Metronidazole IV x 3 days, Ampicillin + Metronidazole PO x 10 days after discharge	Unclear randomization, several drop outs of study, US only utilized for antibiotic group, unsure if post-operative antibiotics given
Styrud, 2006	252 (128[a], 124[s])	Clinical	Cefotaxime + Tinidazole IV x 2 days, Ofloxacin + Tinidazole PO x 10 days after discharge	Males only, unsure if post-operative antibiotics given
Erikkson, 1995	40 (20[a], 20[s])	Clinical + US	Cefotaxime + Tinidazole IV x 2 days, Ofloxacin + Tinidazole PO x 8 days after discharge	No antibiotics given prophylactically

Table 4. Findlay et al Outcome Measures and Conclusions

Outcome Measures	Authors Conclusion
Treatment Efficacy	Surgery Favored
Complications	No Difference
Length of Stay	Surgery Favored (Shorter Length of Stay by .48 days)
Cost	Unclear
Inflammatory Response	Antibiotics Favored
Sick Leave	Antibiotics Favored

Kessler et al (2017) investigated five studies comparing treatment of acute appendicitis with appendectomy versus antibiotics in children <18 years old[13]. The authors excluded studies with patients with complicated appendicitis and children who were immunocompromised. A total of 189 participants were randomized to the antibiotic treatment group while a total of 253 patients were in the appendectomy group (Table 5). Every study utilized ultrasound as an imaging modality, however some studies utilized additional resources such as CT scan or MRI (Table 5).

Kessler et al found that overall treatment efficacy was 98% for the group treated with appendectomy and 74% with the group treated with antibiotics (95% CI 0.71 to 0.84, P<.001). Treatment efficacy was defined as lack of complications and readmission. Antibiotic treatment was found to be associated with a seven times higher risk of readmission compared to the group who underwent appendectomy (95% CI 2.07 to 23.6, p<.001). Researchers also found that complications were comparable between patients who underwent appendectomy and patients who underwent treatment with antibiotics (95% CI .26 to 4.46). Kessler et al found decreased cost and fewer disability days were taken when patients were treated with antibiotics alone. A summary of the results is seen below in Table 6.

Kessler et al also compared patients who had a faecolith to those who did not and found patients without a faecolith had superior outcomes. The same patients without a faecolith also had lower readmission rates (RR .45, 95% CI .28 to .73) and less complications (RR .33, 95% CI .04 to 2.95) compared to patients with a faecolith. However, even the patients with no faecolith treated with antibiotics still had high rates of re-admission (RR 6.28, 95% CI 1.44 to 27.5) and a decreased treatment efficacy (RR .80, 95% CI .73 to .88). Antibiotic usage varied among the groups (Table 5).

Table 5. Kessler et al Study Characteristics

Author, Year	Population	Imaging Modality for Diagnosis	Antibiotics	Risk of Bias
Hartwich, 2015	74 (24[a], 50[s])	US, MRI	Piperacillin-Tazobactam IV; Amoxicillin-Clavulanic Acid x 7 days after discharge	No postoperative antibiotics (even with evidence of contamination), age >60 years old or significant systemic illness excluded
Minneci, 2015	102 (37[a], 65[s])	US, CT	Pip/Tazo or Ciprofloxacin, Metronidazole IV; Amoxicillin-Clavulanic Acid, Ciprofloxacin, Metronidazole x 9 days after discharge	Oral antibiotics used except if the patient was nauseous or vomiting

Mudri, 2017	54 (26[a], 26[s])	US	Ciprofloxacin, Metronidazole IV; Amoxicillin-Clavulanic Acid x 7 days after discharge	Cross-over allowed after randomization if patient/surgeon requested
Svensson, 2015	50 (24[a], 26[s])	US, CT	Meropenem, Metronidazole IV; Ciprofloxacin, Metronidazole x 8 days after discharge	Unclear randomization, several drop outs of study, US only utilized for antibiotic group, unsure if post-operative antibiotics given
Tanaka, 2015	164 (78[a], 86[s])	US, CT	Cefmetazole x 2 days, if no decrease of WBC x 25% then ampicillin-sulbactam, Ceftazidime or Meropenem, or Imipneme-Cilastatin, Gentamicin	Males only, unsure if post-operative antibiotics given

Table 6. Kessler et al Outcome Measures and Conclusions

Outcome Measures	Authors Conclusion
Treatment Efficacy	Surgery Favored
Complications	No Difference
Risk of Readmission	Surgery Favored (lower risk of readmission)
Cost	Antibiotics Favored
Disability Days	Antibiotics Favored

Cost

Only a few of the studies investigated analyzed cost differences between appendicitis treated with appendectomy versus antibiotics. In the studies investigated, cost differences between appendectomy versus antibiotics were variable. Findlay et al found one study that showed cost to be decreased with antibiotic treatment (17.7% reduction) while another study found cost to be comparable for both antibiotic and surgical treatment [12]. Kessler et al found most studies showed cost to be decreased and one study reporting costs to be the same between both treatments[13]. Only one study investigated by Rocha et al analyzed cost, and researchers found conservative treatment with antibiotics to be cheaper by $1,257 USD[11]. The length of time for measurement of cost was not specified.

Inflammatory Response

Only Findlay et al and Rocha et al investigated inflammatory response to conservative (antibiotic) versus surgical treatment. One study investigated by Findlay et al found that there was no difference with CRP between treatment with appendectomy versus antibiotics, however did find white cell count to be reduced initially when patients were treated with antibiotics as opposed to surgery[12]. Temperature was also found to be decreased in Days 1 and 2. Rocha et al measured inflammatory response based upon neutrophil count, C-reactive protein levels, and temperature curve and found all three to be significantly reduced in the group receiving antibiotic treatment[11]. Kessler et al did not investigate inflammatory response[13].

Risk of Readmission

All three studies investigated found patients who received conservative treatment to have an increased risk of readmission to the hospital up to one year [11–13]. Rocha et al found this percentage of readmission to be up to 20%[11]. Kessler et al showed up to a seven times greater risk of readmission with treatment with antibiotics compared to appendectomy[13]. Readmission to the hospital included complications and recurrence of appendicitis.

Pain

Both Rocha et al and Findlay et al reported that majority of the studies investigated showed decreased pain and usage of pain medication in the patients who received antibiotic therapy as opposed to appendectomy [11,12]. One study investigated by Findlay et al found no differences in pain, while two additional studies reported decreased duration of pain with antibiotic treatment [12]. Another study investigated by Findlay et al found less morphine was used with antibiotic treatment. Of note, 584 out of 818 (71.4%) of the procedures completed in this study were performed as open procedures [12]. Rocha et al also found that less pain medication was used in patients treated with antibiotics versus patients treated with appendectomy[11]. Kessler et al did not discuss pain in their study[13].

Length of Stay, Return to Work, and Sick Leave

Findlay et al found that antibiotic usage was associated with fewer sick days taken compared to appendectomy. Interestingly, Findlay et al also found that antibiotic usage was also associated with a longer length of hospital stay, although the mean difference was only .48 days (95% CI 0.10 to 0.85 days) compared to appendectomy[12]. Rocha et al also found patients who received conservative treatment had a faster return to work compared to the group who underwent appendectomy (95% CI-6.99, -3.40 days)[11]. Kessler et al found that treatment with antibiotics led to fewer disability days compared to surgical intervention[13].

Summary

A total of three systematic reviews met the inclusion criteria stated above. Two systematic reviews investigated participants >16 years of age, while the other systematic review investigated participants <18 years of age (Table 7). All systematic reviews had at least a one year follow up with patients. Rocha et al found that conservative treatment of appendicitis with appendectomy was successful 60% (95% CI not specified) of the time [11], Findlay et al found it successful 71% (antibiotic failure 29% of the time, with 95% CI 23% to 34%), of the time and Kessler et al found it successful 74% (95% CI 0.71 to 0.84, p <0.001) of the time (Table 7)[13]. Comparatively the success rate of appendicitis ranged above 90% in all the studies investigated [11–13]. Success was measured as no appendicitis recurrence within 1 year and discharge from the hospital without appendectomy in Rocha et al. Of note, Findlay et al found antibiotic successful in treatment 91% of the time initially, then at the 1 year follow up found this decreased to 71% by the one year follow up[12]. The quality evaluation for efficacy of treatment of appendicitis with appendectomy versus antibiotics is seen below in Table 8.[1] Of note, definitions of efficacy were not clearly specified by Findlay et al and Rocha et al.

Table 7. Study Design, Population Parameters, and Primary Outcome and Results of the Studies Chosen

Study	Number of Studies	Number of Subjects	Population Parameters	Outcome and Results
Rocha et al 2015[11]	8 Systematic Reviews	1,624	Age >18 years	Treatment with antibiotics successful in 60% of patients compared to >90%

				with appendectomy.
Findlay, et al 2015[12]	6 RCTs	1,724	Age >16 years	Treatment with antibiotics successful 71% at 1 year
Kessler, et al 2016[13]	5 RCTs	442	Age <18 years	Treatment with antibiotics less efficacious at 74% compared to 98% with appendectomy

Table 8. Grading the Evidence for the Efficacy of Treatment for Appendicitis Across the Systematic Reviews

	Inconsistency	Indirectness	Imprecision	Risk of Bias	Limitations	Quality
Findlay et al 2015	**High Risk**[1]	**Moderate Risk**[2]	**Low Risk**	**High Risk**[3]	**High Risk**[5]	**Very Low**
Kessler et al	**High Risk**[1]	**Low Risk**	**Low Risk**	**High Risk**[6]	**High Risk**[5]	**Very Low**
Rocha et al 2017	**Moderate Risk**[8]	**Low Risk**	**Low Risk**	**High Risk**[7]	**High Risk**[5]	**Low**

1. Rated as high risk due to high heterogeneity (i2 > 80%) in the studies 2. Rated as moderate risk due to variations in diagnostic criteria, inclusion, and exclusion criteria 3. Rated as high risk due to unclear randomization and unclear reporting of complications. Rated as moderate risk due to varying population parameters 5. Rated as high risk due to low quality of studies investigated and varying antibiotics 6. Rated as high risk due to allocation bias, variety of protocols within the studies 7.Rated as high risk due to selection bias from unblinded outcomes and crossover rate 8. Rated as moderate risk due to moderate heterogeneity and variation

Discussion

Key Findings:

Overall treatment efficacy for acute appendicitis using antibiotics ranged from 60% to 74% (Table 7). Cost differences between the two treatments was variable. Treatment with antibiotics was found to have decreased inflammatory response, faster return to work, and decreased pain. Treatment with antibiotics was also found to have a higher rate of readmission compared to appendectomy, with one study showing up to a seven times greater risk [11–13].

Limitations and Strengths:

A strength of this paper is that only systematic reviews were investigated and a larger sample size was used to determine the outcomes. However, this also introduces design-related bias as each of the papers investigated by the systematic reviews had varying inclusions/exclusion criteria, methods, and outcome measures, even if the difference between some was found to be very slight. Additional risks of bias included variable randomization between the participants and selection bias. The majority of the procedures were performed as open procedures, which introduces another source of potential bias, as the standard of care today is generally seen as laparoscopic appendectomy. Open procedures are associated with a higher risk of complications compared to laparoscopic and may also have increased pain and longer time away from work [14].

One large limitation of all studies investigated is the antibiotic variability used (Table 3 and 5). The differences in antibiotics included dosing differences, length of treatment time, medication variations, and administration route. This has the potential to play a large role in the treatment efficacy if one antibiotic regimen was more effective compared to another. Additionally, imaging modalities for diagnosis of appendicitis varied from ultrasound to CT scan. Ultrasound has a diagnostic rate of 71-97% while CT scan accuracy is between 93-97%. CT scan is more specific for the diagnosis of acute appendicitis and this could have played a role in the overall results as well[15]. If a person was inaccurately diagnosed with appendicitis as a false positive, this could lead to over-treatment and affect the accuracy of the overall results of the studies included. Another limitation that should be noted is the overall quality of the studies investigated was found to be low to very low based on the information above (Table 8).

Another aspect to consider in treatment of appendicitis with appendectomy versus antibiotics is the complications and length of follow-up time. All the studies investigated followed patients for at least one year, however no patient was followed for >4 years. As Kessler et al discussed, post-surgical adhesions may take many years to form. Therefore, 1-4 years may not be an adequate amount of time to accurately determine the total complications that have occurred.

Clinical Importance:

Although antibiotic treatment may be appealing due to the potential of decreased cost, decreased pain at treatment, and decreased inflammatory markers, the rate of hospital readmission and treatment efficacy is worrisome. Additionally, delayed appendectomy may prove to be more complex than if the appendix is removed at the initial episode of appendicitis. Saluja et al completed a retrospective study that found children who underwent late appendectomy for treatment of complicated appendicitis were more likely to have complications[6]. Of note, this was for children with complicated appendicitis so it is unclear if this is applicable to all patients with appendicitis.

Conclusion and Future Directions

Although antibiotic treatment for appendicitis may be as effective as appendectomy in the short-term and also associated with decreased inflammatory markers and a faster return to work, these studies found that it has a high rate of readmission to the hospital. At this time, the evidence supports that surgical intervention through appendectomy remains the standard for treatment of appendicitis. Conservative treatment of appendicitis with antibiotics should be reserved for special cases if patients are strongly opposed to surgery. If this is the case, patients should be made aware of the decreased efficacy and risk of readmission with antibiotic treatment. More studies need to be completed with laparoscopic procedures and longer follow up duration in order to accurately determine if antibiotics can become a safe alternative for treatment of acute appendicitis.

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Appendix

Table I. Rocha et al Participants, Studies Included, and Grading of Evidence

Author (Year)	Participants	Studies Included	Quality Evaluation
Varadhan et al (2010)	661 (350[a], 311[s])	3	2.7[1]
Liu et al (2011)	1201 (433[a], 786[s])	6	>5[2]
Ansaloni et al (2011)	741 (390[a], 351[s])	4	Poor
Wilms et al (2011)	901 (415[a], 486[s])	5	Low-Moderate
Mason et al (2012)	980 (510[a], 470[s])	5	1.8[3]

Table II. Findlay et al (2015) Grading of Evidence

Analysis	Studies (Number of Patients)	Risk of Bias	Directness	Consistency	Precision	Publication Bias	Overall
Successful Treatment	6 studies (1724 patients)	**High Risk; Very Serious[1358]**	**Serious Limitation[67]**	**None**	**None**	**None**	**Very Low**
Complicated Appendicitis	6 studies (1641 patients)	**High Risk, serious limitations[123458]**	**Serious limitations[67*]**	**None**	**None**	**None**	**Very Low**
Complications							
Minor and Major Complications	6 studies (1724 patients)	**High Risk, very serious limitations[12459*]**	**Serious limitations[67]**	**None**	**None**	**None**	**Very Low**
Length of stay and Sick Leave	6 studies (1724 patients)	**High risk, very serious limitations[1245*]**	**Serious limitations[67*]**	**None**	**None**	**None**	**Very Low**

1. **Unclear randomization 2. Randomization completed by date of birth 3. Incomplete follow-up 4. Incomplete follow up 5. Variable inclusion criteria 6. Variable antibiotic therapy 7. Variable identification of complicated appendicitis 8. Complications not defined 9. Complications may have been reported selectively *. large protocol violations**